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REVIEW

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Childhood obesity: Implications on adipose tissue dynamics and metabolic health

Ivonne Palacios-Marin[1,2] | Dolors Serra[2,3] | Josep C. Jiménez-Chillarón[1,4] | Laura Herrero[2,3] | Marijana Todorčević[2]

[1]Endocrinology Department, Institut de Recerca Sant Joan de Déu, Barcelona, Spain

[2]Department of Biochemistry and Physiology, School of Pharmacy and Food Sciences, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona (UB), Barcelona, Spain

[3]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain

[4]Department of Physiological Sciences, School of Medicine, Universitat de Barcelona, L'Hospitalet de Llobregat, Catalonia, Spain

Correspondence
Josep C. Jiménez-Chillarón, Department of Physiological Sciences, School of Medicine, Universitat de Barcelona, L'Hospitalet de Llobregat, Catalonia, Spain.
Email: josep.jimenez@sjd.org; josep.jimenez@ub.edu

Laura Herrero, Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, E-28029 Madrid, Spain.
Email: lherrero@ub.edu

Marijana Todorčević, Department of Biochemistry and Physiology, School of Pharmacy and Food Sciences, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona (UB), E-08028 Barcelona, Spain.
Email: mtodorcevic@ub.edu

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Summary

Obesity is the leading risk factor for the development of type 2 diabetes and cardiovascular diseases. Childhood obesity represents an alarming health challenge because children with obesity are prone to remain with obesity throughout their life and have an increased morbidity and mortality risk. The ability of adipose tissue to store lipids and expand in size during excessive calorie intake is its most remarkable characteristic. Cellular and lipid turnovers determine adipose tissue size and are closely related with metabolic status. The mechanisms through which adipose tissue expands and how this affects systemic metabolic homeostasis are still poorly characterized. Furthermore, the mechanism through which increased adiposity extends from childhood to adulthood and its implications in metabolic health are in most part, still unknown. More studies on adipose tissue development in healthy and children with obesity are urgently needed. In the present review, we summarize the dynamics of white adipose tissue, from developmental origins to the mechanisms that allows it to grow and expand throughout lifetime and during obesity in children and in different mouse models used to address this largely unknown field. Specially, highlighting the role that excessive adiposity during the early life has on future's adipose tissue dynamics and individual's health.

KEYWORDS
adipocyte turnover, adipose tissue, childhood obesity, lipid turnover

Abbreviations: ^{15}N-, ^{15}N-thymidine; APCs, adipocyte progenitor cells; AT, adipose tissue; BAT, brown adipose tissue; BMI, body mass index; CD36, cluster of differentiation 36; CVD, cardiovascular disease; db/db, Leprdb/Leprdb mouse; DNL, de novo *lipogenesis*; E, embryonic; eWAT, epididymal white adipose tissue; HFD, high-fat diet; iBAT, interscapular brown adipose tissue; iWAT, interscapular white adipose tissue; LPM, lateral plate mesoderm; MSCA1, mesenchymal stromal cell antigen-1; Mx1+, myxovirus 1; *Myf5*, Myogenic factor 5; P, postnatal; *Pax3*, Paired box protein Pax-3; *Pax7*, Paired box protein; pgWAT, perigonadal white adipose tissue; scWAT, subcutaneous white adipose tissue; SVF, stromal vascular fraction; *Tagln*+, transgelin; TAG, triacyclglycerols; T2D, type 2 diabetes; vWAT, visceral white adipose tissue; WAT, white adipose tissue; WT, wild type; *Wt1*$^{+}$, Wilms tumor protein 1; WHO, World Health Organization; Wt1+, Wilms tumor protein 1.

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1 | INTRODUCTION

Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health.[1] Clinically, in adults, it is assessed through the body mass index (BMI: weight [kg]/height[m^2]). Anyone with a BMI between 25 and 30 is classified as with overweight and anyone with a BMI higher than 30 kg/m^2 is classified as with obesity. Quantifying obesity in children is different than in adults because children are still growing.[2] Nutritional status is assessed through different anthropometric indexes depending on the children's age. From birth to 24 months of life, the weight-for-length ratio is normally used; whereas after the age of two, the weight-for-height and BMI-for-age become more commonly employed.[3–5] In all cases, children are categorized as underweight if they are located below the 5th percentile, from 5th to 84th percentile is considered healthy weight, and between 85th and 94th percentile is with overweight whereas above 95th is with obesity.[2,3] After the age of two, severe obesity can be diagnosed in those children located above the 99th percentile.[3–6] Although these indexes are not ideal to assess adiposity because neither of them account for body fat percentage, it has been described that levels above the 95th percentile of BMI-for-age in children are associated with increased adiposity in 65% of the cases; which raises up to 94% in children located above the 99th percentile.[7,8]

According to the World Health Organization (WHO), the incidence of obesity has tripled since 1975 within adult population. Additionally, the prevalence of obesity shows significant variation among various ethnic backgrounds.[9] The most worrying observation is the increase of obesity among pediatric population. The prevalence of obesity has risen dramatically in both children and adolescents aged 5–19 years, from 4% in 1975 to over 18% in 2016.[1] In 2019, around 38.2 million children under the age of 5 years were identified with overweight or obesity.[10] This issue impacted almost one in three children, with approximately 29% of boys and 27% of girls being affected, within the WHO European Region (WHO, 2022).[11] Childhood obesity represents a serious public health challenge because it has been shown that nearly 55% of children with obesity will remain with obesity during adolescence and about 80% of adolescents with obesity will still suffer from this condition in the adulthood.[7,8,12] In adult population; robust epidemiological studies have established that the risk of adverse metabolic comorbidities, such as type 2 diabetes (T2D), cardiovascular disease (CVD), and mortality increase linearly as BMI increases.[13–16] Children with obesity have also a higher risk of developing similar comorbidities later in life, including disabilities and premature death.[7,8,17,18] It is still unclear how excessive adiposity, when it develops during childhood and adolescence, exert long-term metabolic disturbance, as well as into adulthood. Due to complex mechanisms that drive this phenomenon, little has been described about it in the literature. The aim of this review is to outline key aspects regarding the current knowledge on adipose tissue (AT) development and dynamics in children as well as potential mechanism that lead to obesity and obesity related disorders from intrauterine period to extrauterine life.

2 | AT FUNCTIONS

AT is a multitasking organ with a central role in energy and metabolic homeostasis, regulation of appetite, thermoregulation, immunity, and secretion of different endocrine factors. AT depots are widely distributed around the body. In mammals, AT is mainly found in anatomically distinct body compartments; subcutaneous (mainly found under the skin) and visceral (among internal organs). Furthermore, AT can be differentiated as either white, brown, pink, and beige.[19] White AT (WAT) is composed mostly of adipocytes containing a large unilocular lipid droplet and it is mainly involved in energy storage and mobilization as well as secretion of adipokines.[20] Under an energy metabolic imbalance, the consequent disrupted adipokine secretion frequently contributes to AT dysfunction and obesity development. Brown AT (BAT) is specialized in energy expenditure and fat burning. Brown adipocytes are rich in mitochondria and multiple smaller (multilocular) lipid droplets. Recently, a third type of adipocytes were described: the brown-in-white ("brite") or beige adipocytes. These thermogenic adipocytes show an intermediate *Ucp1* expression compared with white or brown adipocytes and arise within the WAT under a specific stimulus such as the beta-adrenergic stimulus in a process called "browning." Beige adipocytes are found within the WAT of both human and mice. Beige adipocytes have an overlapping, but also a distinct gene expression pattern compared with classic brown adipocytes.[21,22] Beige AT has metabolic properties similar to BAT, including the ability to utilize glucose and fatty acids for thermogenesis.[23] Thermogenic brown and beige AT gained a lot of interest as potential therapeutic targets for obesity.

Finally, females have one extra type of adipocytes called pink adipocytes, which are milk-secreting alveolar cells that derive from the

trans differentiation of subcutaneous white adipocytes only during pregnancy, lactation, and post-lactation.[24,25]

Different types of AT perform different metabolic functions and exhibit differences at cellular and structural levels. Anatomic location plays a critical role in metabolic diseases. AT distribution is variable between individuals.[26] Each fat depot has different metabolic functions as well as different molecular and physiological features. In mammals, WAT is classified according to its location into subcutaneous WAT (scWAT) and visceral WAT (vWAT).[27] In humans, scWAT is located at the retro-orbital, facial, abdominal, subcutaneous, and gluteal areas while in rodents it is located at the suprascapular, anterior, inguinal, and gluteal areas. vWAT in humans is found at the retroperitoneal, perirenal, omental, and mesenteric areas while in rodents, it is found at the gonadal, perirenal, and retroperitoneal areas. Human BAT develops in the early stages of life and declines during growth.[28] In newborns, it is found mainly in the interscapular, perirenal, buccal pad (first 2 weeks of life), supraclavicular, paravertebral, axillar, cervical, and per-aortic areas. The main locations of BAT in rodents are the anterior cervical, supraspinal, supraclavicular, infrascapular, interscapular, axillar, perirenal, and paravertebral. Developmental transitions from infancy to childhood to adolescence are associated with changes in the pattern of growth of AT depending on location and sex. The mechanisms by which AT distribution is patterned in children is a major gap in knowledge.

3 | DEVELOPMENTAL ORIGINS OF AT

AT development is a very complex and dynamic process. The first longitudinal histological assessment of mouse embryonic development was done by Flemming in the 1870s, and the authors demonstrated that significant percentage of adipocytes emerged from mesodermal-derived connective tissue.[29,30] However, the recent studies of AT lineage hierarchy have revealed that adipocyte's ontogeny is even more complex than previously thought[29–32] and that a small subset of adipocytes differentiate from neural crest cells, which are of ectodermal origin,[33,34] thus, suggesting that the specific developmental origin of adipocytes may differ between locations.

During gastrulation the epiblast differentiates into three primary germ layers: the endoderm, the mesoderm, and the ectoderm.[35] In later stages of embryogenesis, cells of these three germ layers differentiate and give rise to a specific set of tissues and organs.[36] Depot-specific adipocyte lineages spatially diverge as early as during gastrulation. After gastrulation, the mesoderm divides into three subcompartments: the somites, the lateral plates, and the intermediate mesoderm.[37] Most of the body adipocytes arise from these three subcompartments (Figure 1A). During somitogenesis, the potency of the cells is progressively being restricted so they can acquire an "identity." Somitic cells differentiate into three different domains: the sclerotome, the myotome, and the dermomyotome.[37] From them, the dermomyotomal progenitors had shown to have the greatest flexibility in cell fates.[29,30,38]

Recent studies in mammals have shown that AT depots are heterogeneous and that even within the same depot, individual adipocytes could have different developmental origins.[39–41] In agreement with this hypothesis, Sebo et al.,[32] reported that *Paired box protein Pax-7* (*Pax7*$^+$) embryonic progenitors contribute equally to the establishment and maintenance of interscapular BAT (iBAT) and a minority of interscapular white adipocytes in mouse (iWAT). Several in vivo fate mapping studies described that *Myogenic factor 5* (*Myf5*$^+$) lineage gives rise to brown and white adipocytes and that the percentage of adipocytes descendants from *Myf5*$^+$ varied within depots.[40] Interestingly, authors found that *Paired box protein Pax-3* (*Pax3*$^+$) largely overlaps with *Myf5-lin*$^+$ in several scWAT depots.[31] These findings suggest that allocation of somitic progenitors to vWAT, scWAT, or BAT depots may be better explained by their physical location along the dorsoventral axis of the dermomyotome during embryogenesis. Appropriate developmental patterning of AT results in a stereotyped anatomical configuration of white and brown fat depots.[38] Due to its recent and still incomplete characterization, the origins of beige adipocytes are less clear; nevertheless, the evidence supports the notion that some Myf5-lin + adipocytes may transform into beige adipocytes, while others may arise de novo from Myf5-lineage precursors.[31] The embryonic origins of pink adipocytes have not been described, but emerging evidences suggest that they are derived from the transdifferentiation of subcutaneous white adipocytes[24,25]; whether then the transdifferentiated pink adipocytes possess a specific lineage or form a specific subpopulation is still unknown.

Lateral plate mesoderm (LPM) compartment forms two bilateral symmetrical sac-like structures that fill the presumptive abdominal region of the embryo, and it is divided into two layers: the splanchnic and the somatic layers.[32] A meticulous tracing of LPM progenitors showed that the splanchnic layer of the mesoderm contributes to form vWAT depots, while the somatic layer gives rise to the subcutaneous and supra-muscular limb-associated adipose depots.[32,42] Recently, it was reported that visceral fat depots both in mice and humans express Wilms tumor protein 1 (Wt1+), while the expression was absent in subcutaneous fat depots.[43] In line with other in vivo fate mapping reports,[31,32] the authors concluded that Wt1-lin+ contributed to the adipocyte progenitor cells (APCs) pool of several vWAT depots in mice, and that the percentage of Wt1+ descendant adipocytes varied among depots.[43] Further in vivo lineage tracing experiments have shown that lineage heterogeneity in adipocytes correlates with size heterogeneity,[31] suggesting that this might play a role in adipocyte function, location, and phenotype. Similar to these findings, several studies have indicated that in humans, WAT depots exhibit a diverse lineage composition of adipocytes among individuals within the same depot. Remarkably, this heterogeneity has been found to be closely associated with the size of the adipocytes.[39,44,45] It has also been proposed that adipocyte lineages might maintain some degree of flexibility throughout lifetime and that some lineages, for example, the Myf5-lineage, selectively expands in response to environmental factors like a high-fat diet (HFD)[31]; suggesting ontogeny as a possible driver behind the ability of adipocytes to transdifferentiate.

In a recent study by Lee et al.,[41] three distinct subpopulations of white preadipocytes were identified based on the expression of specific marker genes: Wt1+, transgelin (Tagln+), and myxovirus

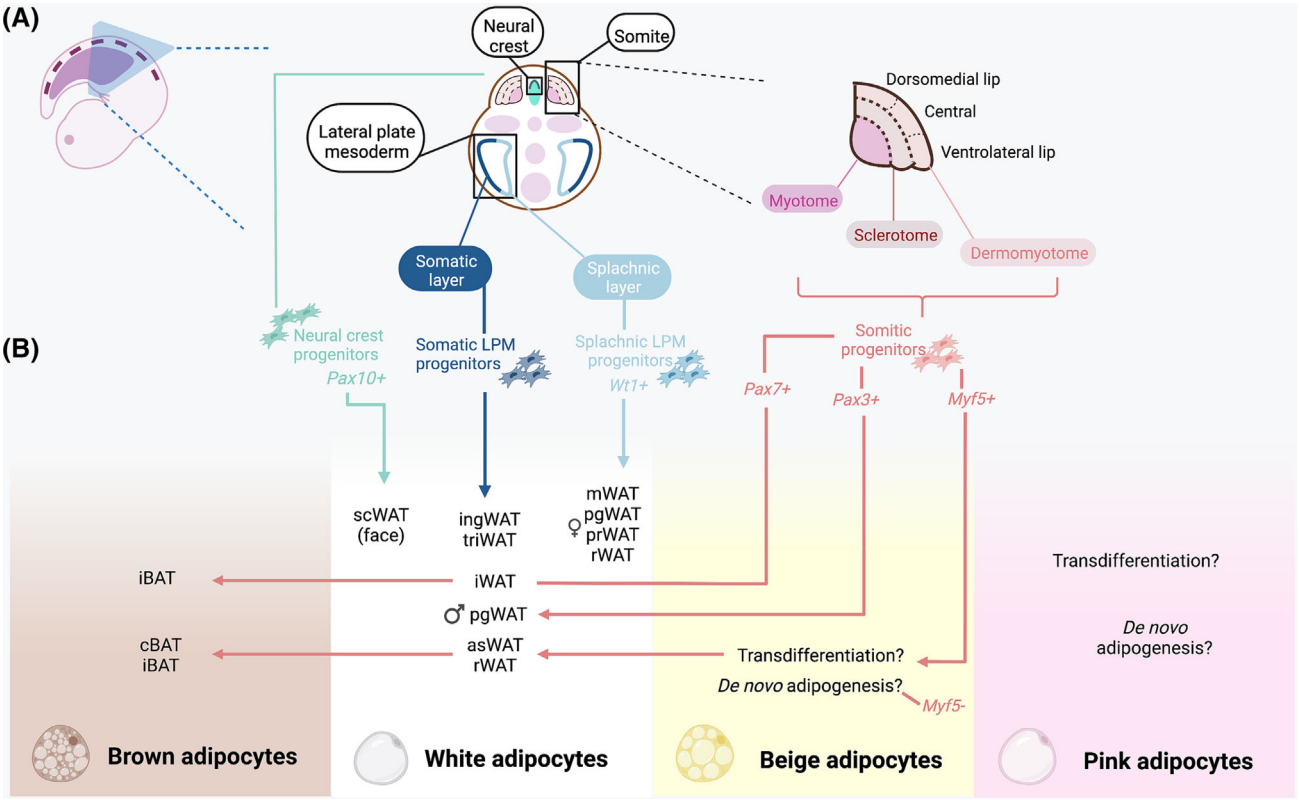

FIGURE 1 Adipose tissue ontogeny. (A) Cross-sectional view of a mouse embryo showing mesodermal and endodermal compartments from which adipocytes arise. (B) Adipocyte lineage tree based on current lineage-tracing data in mice (arrows indicate cell lineage). Both white and brown adipocytes from different depots derive from somitic progenitors, cells with the most diverse cell fates. Visceral adipocytes derive from the splanchnic progenitor pool of the lateral plate mesoderm. The subcutaneous and supra-muscular limb-associated adipocytes arise from the somatic pool. Finally, scWAT from the face possess endodermic origins because they derive from neural crest progenitors. Anterior subcutaneous WAT (asWAT), cervical BAT (cBAT), inguinal WAT (ingWAT), interscapular BAT (iBAT), interscapular WAT (iWAT), mesenteric WAT (mWAT), perigonadal WAT (pgWAT), perirenal WAT (prWAT), retroperitoneal WAT (rWAT), subcutaneous WAT (scWAT), and tricipital WAT (triWAT).

1 (Mx1+). The distribution of these subpopulations varied across different AT depots. Wt1+ adipocytes were exclusively found in visceral and pericardial AT depots, with the highest concentration observed in perigonadal fat. They were also present in pericardial, perirenal, and mesenteric fat, albeit in lower amounts. Tagln+ adipocytes, on the other hand, were present in all AT depots. The highest abundance of Tagln+ adipocytes was found in pericardial fat, followed by mesenteric, perirenal, and perigonadal fat. However, scapular and inguinal WAT had lower levels of Tagln+ adipocytes. Mx1+ adipocytes were predominantly located in scapular white fat, with smaller numbers also present in inguinal and perirenal fat depots.[41]

The investigation of embryonic cellular lineage tracing in vivo requires the use of sophisticated technologies that are not currently approved for human usage; therefore, the majority of studies focusing on tracing the ontogeny of white WAT have been performed in rodent models.[29,30,36] Our understanding of human AT depot ontogeny has mainly relied on the analysis of tissue expression using various methodologies.[39,43–45] Although significant differences have been reported in the gastrulation process, cell potency, transcription factor complexes, and cell markers between human and mice WAT development,[36,46–49] there are also notable similarities. For instance, both human and rodent WAT depots exhibit distinct gene signatures and metabolic features, suggesting that each depot could be considered as a distinct mini-organ.[41,43] Additionally, both human and rodent WAT depots demonstrate lineage heterogeneity within the same depot, which is correlated with variations in adipocyte size.[39–41,44,45] Taken all together, these findings support the idea that adipocytes from the same depot can arise from different APCs and that ontogeny could determine, at least in part, the metabolic and phenotypic profile of the adipocytes.

Kim et al.[50] assess adipogenesis in vivo during postnatal growth in C57Bl/6 mice. For this, the authors labeled new-born mice at 4-days-old with ^{15}N-thymidine and chased the adipocytes and the stromal vascular fraction (SVF) of visceral and scWAT depots at the end of the labeling period (8 weeks old) and at 20 months old. At 8 weeks old, ^{15}N-labeling was present in 56% and 85% of adipocytes from the sWAT and vWAT depots, respectively, demonstrating that, like in humans, the early life is the period with the higher adipogenesis rate.[50] The lower labeling of subcutaneous adipocytes may indicate that these adipocytes started the commitment much earlier in life than visceral adipocytes, which is also in line with other reports.[51–53] After the 18-month chase, SVF and adipocyte labeling in the vWAT depot was drastically reduced, suggesting a moderate turnover rate in

adult mice. Strikingly, sWAT displayed an increase in the ^{15}N-labeled adipocytes during the 18-month chasing; the authors provided various possible explanations, ranging from a selective death from nonlabeled adipocytes to the possibility that new adipocytes could have arisen from previously labeled APCs.[50] Overall, current data suggest that the late pregestational and early postnatal life are the most important periods for adipocyte acquisition; after which, scWAT of mice shows a similar turnover rate like adult humans whereas visceral adipocytes in mice showed a much higher adipocyte turnover, suggesting important differences between species. Independently, existing evidence suggest that hyperplasic capacity of WAT decreases with aging. Overall, these findings highlight the relevance of the early postnatal life (i.e., early childhood) in the adequate development of WAT and the possible physiological consequences that an increased adiposity during this fundamental life period may have.

4 | FROM MESENCHYMAL STEM CELLS TO ADIPOCYTES

Adipogenesis is a dynamic process tightly regulated. Two different phases of adipogenesis have been established in vitro: adipogenic lineage determination and terminal differentiation.[54] In the first phase, pluripotent stem cells commit to the adipocyte lineage and lose their ability to differentiate into other cell types. Committed preadipocytes undergo growth arrest and subsequent terminal differentiation into adipocytes[55] (Figure 2). Transcriptional events that accompany the late stages of terminal adipocyte differentiation have been extensively studied while the early molecular events that control the lineage determination of early precursor cells are still poorly understood.

Developmental pathways involved in adipogenesis in vivo are far less studied because they involve a set of complex events influenced by genetic, hormonal, and nutritional factors. In addition, an increasing number of studies have suggested that adipocyte precursor cells are different in fetus and adults and that adipogenesis is differently regulated.[52]

Fetal adipogenesis begins with the determination of embryonic stem cells, which give rise to adipocytes. Only a few molecules involved in prenatal adipogenesis, such as ZFP423, perilipin, adiponectin, mesenchymal stromal cell antigen-1 (MSCA1), and cluster of differentiation 36 (CD36), have been identified so far. Shao et al. showed that ZFP423 is essential for the terminal differentiation of subcutaneous white adipocytes during fetal AT development in mice.[56] Surprisingly, the whole process is C/EBPα independent, even though C/EBPα is a very important transcription factor for adult adipogenesis.[57] In addition, embryonic preadipocytes are shown to express perilipin and adiponectin.[53] The authors concluded that embryonic preadipocytes use the expression of these two transcription factors in order to expand the adipose-lineage cell population. A recently published study by Hanschkow et al. suggested that mesenchymal stromal cell antigen-1 (MSCA1) and cluster of differentiation 36 (CD36) serve as important adipocyte progenitor markers and play a significant role in the functioning of AT in children. This research emphasizes the importance of these markers in understanding the mechanisms underlying AT function in pediatric populations.[58] More research understanding fetal adipogenesis is urgently needed, especially considering that the increase in the obesity and metabolic syndrome may have its origins in utero.[59]

5 | DYNAMICS OF AT: FROM INTRAUTERINE TO ADULTHOOD

Alarming raising in obesity prevalence has triggered the interest in the study of the WAT dynamics, which is a complex interplay between adipocyte number, adipocyte size and adipocyte replacement. The current understanding of WAT dynamics in humans is still very limited for several reasons: First, the obesity epidemic is a relatively recent event in human history. Second, the development of excessive adiposity is generally slow, gradual, and frequently proceeds through very long periods of life-course, which limits longitudinal studies. Finally, the post-mitotic nature of adipocytes makes it difficult to design proper in vivo studies, which would help understand cellular dynamics within the AT. Despite these limitations, both human and animal studies show that the expansion of WAT in response to excessive caloric intake can happen during any life stage.[51,60–62]

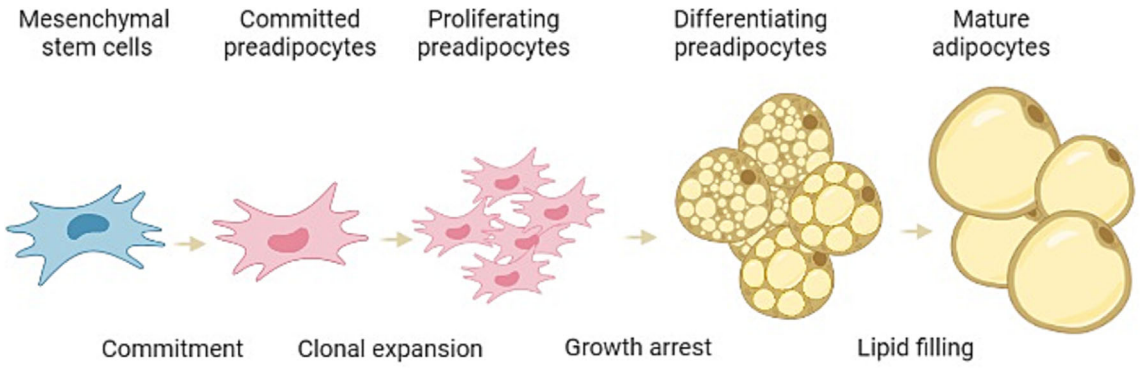

FIGURE 2 From mesenchymal stem cells to adipocytes. An overview of the stepwise progression from mesenchymal stem cells to mature adipocytes, highlighting the key molecular events involved in the adipocyte differentiation pathway.

In addition to dietary imbalances, childhood obesity is influenced by genetic and epigenetic factors as well as by numerous social and economic determinants, including ethnicity. There is growing concern about the increasing prevalence of childhood obesity among diverse ethnic and racial groups. While childhood obesity rates are rising in all ethnic and racial groups, non-White populations tend to have a higher prevalence. The factors contributing to these disparities in childhood obesity rates are complex and involve genetics, physiology, culture, socioeconomic status, environment, and interconnected variables that may not be fully recognized at this time.[63–65] Emerging evidences suggest that the metabolic status of mothers and maternal nutrition during pregnancy plays a crucial role in determining the metabolic health of the offspring throughout their life.[66] Thus, rodent models of maternal overnutrition/obesity have been developed to study this paradigm, including maternal DIO models and the agouti viable yellow (Avy/a) mouse model.[66–68] Several studies have investigated the relationship between early overfeeding and epigenetic modifications.[69,70] Data from animal models, including maternal DIO mouse models and the Avy/a mouse model[66–68] have shown that overfeeding during early life can lead to changes in the expression of genes involved in metabolism, appetite regulation, energy balance, and insulin resistance.[71–74] Interestingly, reduced DNA methylation in the Zfp-423 promoter and increased gene expression persisted in the offspring of obese dams at weaning, resulting in elevated premature adipogenic differentiation of progenitor cells.[72] This, in turn, limited AT expandability when these offspring were challenged with an HFD, leading to adipocyte hypertrophy, a cause of hypoxia and inflammation.[72] It has also been shown that maternal diet-induced obesity programs increased expression of miR-126 in AT of lean offspring. This was associated with decreased protein abundance of one of its targets, the insulin signaling protein IRS-1.[75]

Children born to mothers with obesity often exhibit an increased risk of developing adiposity, obesity, and metabolic disorders, including insulin resistance, glucose intolerance, and dyslipidemia, not only during childhood but also in adulthood.[69,76] This association has led to the proposal of a connection between early overfeeding and epigenetic modifications. Infants who experienced excessive feeding during the initial months of life exhibited distinct DNA methylation patterns in genes associated with obesity and metabolism, which persisted into later childhood.[77]

Obesity also leads to changes in BAT activity in infants and adolescents. It has been shown that cold-stimulated BAT activity in young children (8–10 years old) with overweight/obesity is lower than in those with normal BMI.[78] Data from infants at birth and at 4 and 12 months demonstrated that BAT activity is sex specific in the first year of life.[79] In this study, the authors showed that posterior cervical BAT activity was negatively associated with adiposity only in girls demonstrating the very early appearances of sex differences in BAT activity. BAT development takes place intra-utero, and it is activated at birth, upon cold and endocrine stimulation.[80,81] BAT formation has been shown to be altered in preterm or small for gestational age infants.[82] During adolescence, BAT development might be influenced by cold exposure, physical activity, and sex hormones.[83]

5.1 | Hypertrophy and hyperplasia

WAT expansion during development is accomplished through combined increase of (1) adipocyte cell size enlargements (hypertrophy) and (2) adipocyte number (hyperplasia).[50,60,84–89] Most data regarding expansion of WAT during human development come from the studies done in the 80s. In humans, WAT depots appear between the 14th and 24th weeks of the fetal development. Adipogenesis is initiated when fetuses' weight is around 125 g and develops gradually; by the 28th week of gestation all major body WAT depots have been formed.[90] After birth, body fat content increases considerably, specially between 0 and 6 months of age. During this period, adipocyte number does not significantly rise. Instead, adipocyte cell size increases rapidly and reaches mean cell diameters similar to adolescence.[87] From 6 months to 2 years of life the rate of weight gain decreases, leading to slight decrease in adipocyte size as well. But the fat mass growth in children with normal weight occurs through small and sustained increases in cell number.[87] At this age, no differences between sexes have been reported. From the age of 2 years to early adolescence, adipocyte cell size does not significantly change in children with normal weight,[87,91] while small but progressive increases in adipocyte number continue to take place.[87,91]

Puberty (≈10–18 years old) is characterized by many important physiological changes including an increase in both, adipocyte size and number, in both genders.[87,91] Furthermore, at this age, there is a recognized gender difference in adiposity.[92] In boys, the increase in body weight is mainly attributed to gains in lean mass, while in girls, it is primarily attributed to gains in fat mass. Additionally, this period marks the onset of typical fat distributions, with boys exhibiting android fat distribution and girls exhibiting gynoid fat distribution for the first time.[92,93] In humans, it is well established that the expansion of lower fat depots in the body is associated with metabolic protection. Conversely, the expansion of upper fat depots poses an increased risk of metabolic consequences commonly associated with obesity.[94] In females, the accumulation of fat in the femoral region is associated with an increase in the number of adipocytes while in males, it is associated with an increase in the size of adipocytes.[95] In both sexes, fat accumulation in the abdominal area is linked to adipocyte hypertrophy. However, even in a lean state, women have a greater number of adipocytes to begin with, allowing them to accommodate a larger fat mass.[91,96,97] Within normal weight conditions, adipocyte number reaches a plateau around 18 years of age, setting the number of these cells for the rest of the adulthood[87] (Figure 3). A correlation between cell number and total body weight, total body fat, and percentage of fat was found in children with normal weight (1–19 year olds),[87] indicating that adipocyte number is a major contributor to the absolute enlargement of fat depots during childhood and adolescence.

In conclusion, current observations indicate that adipocyte number is set early in life and tightly maintained throughout life. Better understanding of the mechanisms behind regulation of adipocyte number would open the path for novel evidence-based therapies for treating obesity and its related comorbidities.

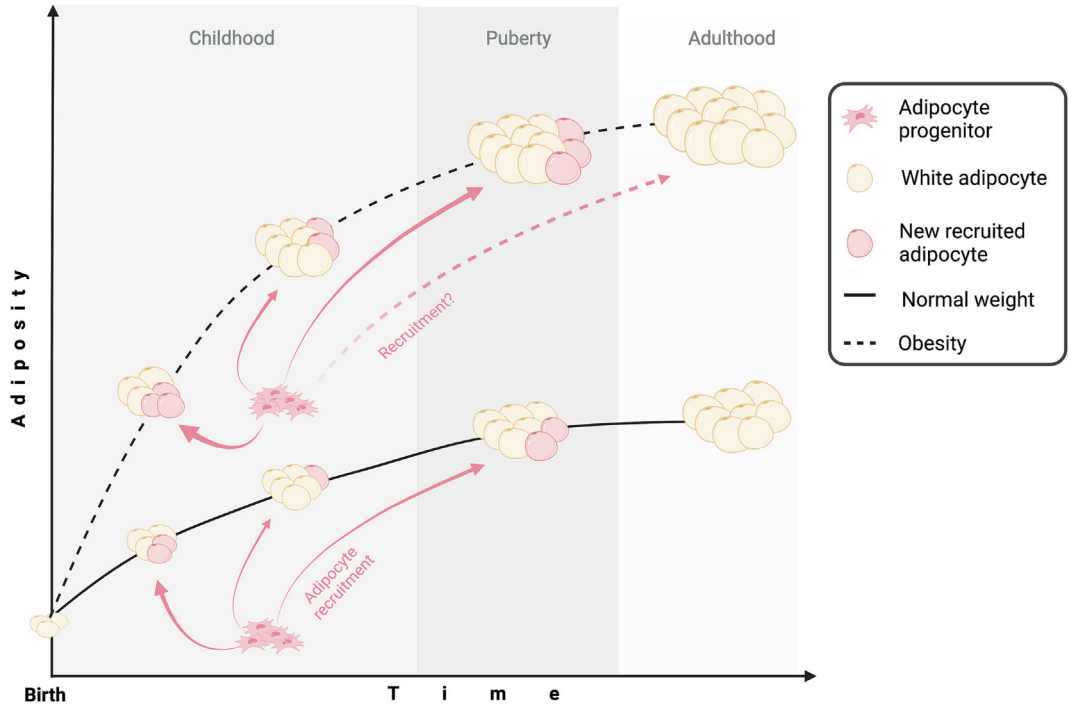

FIGURE 3 White adipose tissue growth in healthy and obesity conditions. After birth, under normal weight conditions (cells joined by a continued line) adipose tissue expands through a coordinated interaction between hypertrophy and small increases in cell number (hyperplasia). After puberty, a plateau in cell number is reached and maintained throughout adulthood. If obesity is established during childhood and puberty (cells joined by dotted lines), a more abrupt increase in both cell number and cell size takes place. Accommodation of excess energy in WAT initially occurs through hypertrophy. If the energy surplus persists, adipocyte progenitors are recruited for subsequent hyperplastic expansion, leading to a higher adipose cell number before entering the stable period of adulthood. Early childhood and puberty are the most important periods for adipocyte recruitment (arrows size represents cell recruitment).

5.2 | Lipid turnover

Adipocyte hypertrophy occurs through lipid accumulation; therefore, lipid turnover must play an important role in determining total fat mass.[98] Lipid dynamics of WAT have been studied in adult population since the 1960s.[99–105] Recently, it was suggested that adipocyte lipid removal rate decreases with aging resulting in weight gain. Importantly, disturbances in lipid kinetics of WAT determined the gain, loss, or maintenance of BW and adipose mass throughout entire adulthood.[103] To our knowledge, no study has, to date, assessed lipid turnover in pediatric population. Positive correlation between adipocyte size and total fat mass in childhood and adolescence suggests that adipocyte lipid kinetics play an important role in determining total fat mass also at this age[87]; thus, the study of the mechanisms through which lipid turnover regulates whole body adiposity and BW during the pediatric age should promptly be addressed.

5.3 | Adipocyte turnover

Adipocyte turnover is subjected to a tight regulation, making the number of adipocyte cells "stable" at any given period of life. Utilizing the release of atmospheric ^{14}C resulting from nuclear testing during the Cold War, Spalding et al (2008) developed a method to evaluate cellular turnover in the human body.[61,106] Although nuclear bomb detonations occurred at specific locations, the increased levels of ^{14}C in the atmosphere rapidly dispersed globally.[107–109] The atmospheric ^{14}C reacted with oxygen to produce CO_2, which in turn was assimilated by plants through photosynthesis. Next, when humans consumed these plants or animals that relied on plants as a food source, the concentration of ^{14}C in their bodies closely mirrored that present in the atmosphere at any given time.[110–112] Given that DNA remains stable after the last instance of cell division, the levels of ^{14}C found within DNA served as a distinctive indicator of cell birth.[106] By measuring the ^{14}C genomic DNA of adipocytes from scWAT, Spalding et al.[61] retrospectively determined the adipocyte kinetics in a large cohort of individuals between 20 and 70 years of age. To estimate adipocyte turnover during life-course, the authors combined their data with previous reports of cellularity from children and adolescents.[113] Interestingly, it was found that adipocyte number leveled off and remained constant during adulthood irrespectively of participant's weight category and BMI. Based on these findings, the authors concluded that differences in adipocyte number among different BMI categories is established earlier in life, during participant's growth period,[61] putting childhood and adolescence in the spotlight for the adequate development of WAT.

Scherer et al. developed a sophisticated triple transgenic doxycycline inducible mouse model (AdipoChaser) that labels mature

adipocytes, allowing with this, to determine the developmental time of adipocyte differentiation in mice.[51] Using this model, they studied the commitment of the adipocyte lineage in scWAT and perigonadal WAT (pgWAT) during fetal and postnatal development until the 56th day of life.[51] Authors reported that pgWAT (vWAT) arouse at a late stage of fetal development, between gestational Days 19 and 20. Importantly, most part of this tissue differentiated gradually during a long period of time after birth, with no differences between male and female mice being reported. In contrast, scWAT started its development earlier in fetal development, between embryonic Days 14 and 18 in both sexes, with most of subcutaneous adipocytes being formed during fetal life. Despite its earlier commitment, scWAT at postnatal day 28th still showed large areas lacking mature adipocytes, suggesting that although subcutaneous adipocytes committed earlier, they need more time for fully differentiate. After this point, the number of cells remains very stable during the postnatal period.[51]

Using yet another transgenic doxocycline inducible mouse model (AdipoTrak), it has been described that developmental and adult adipocytes originate from two different APCs compartments and that they are derived from different lineages.[52,114] These different APCs compartments are sequentially required for WAT formation, homeostasis, and maintenance throughout lifetime.[52,114] According to the authors, developmental APCs from the scWAT depots appears between embryonic (E) Day 14.5 and postnatal (P) Day 2; whereas vWAT depots develop later, between E18 and P20. Strikingly, adult APCs compartment appears to be specified earlier at E10.5.[52] Interestingly, it has been reported that the proliferation of the APCs increases as the embryo get closer to birth; however, after birth, proliferation sharply decreased while cell size expands.[53] The authors found that embryonic and adult APCs evolve from two different progenitor populations, as reported by others.[52,114]

6 | OBESITY IN PEDIATRIC AGE

The level of AT accumulation during childhood is closely related to adult adipocyte number. Several research groups suggested that the final number of adipocytes is set during this period and strictly controlled thereafter[115]; however, additional studies are necessary to support this idea.

It has been described that children with obesity of all groups of age (1–19 years) showed larger adipocytes than the normal weight counterparts,[87,116] and a correlation between adipocyte size and percentage of body WAT during this life period has been found,[87] suggesting that adipocyte hypertrophy plays an important role in pediatric obesity. Remarkably, between Years 1 and 2, when normal weight children display a marked decrease in adipocyte size, children with obesity displayed significant increments in lipid content, reaching as early as age two an adult adipocyte's size.[87] Further, the hypertrophic expansion of WAT has been reported throughout the entire childhood, although in a more modest rate. Interestingly, after the age of 17 years, children with obesity displayed a more abrupt cell enlargement than in earlier life stages.[87] Regarding cellularity, conversely of what was described in children with normal weight, children with obesity showed significant increases in cell number at all age groups (1–19 years old).[87] Two distinct periods have been reported to have a special importance regarding hypercellularity growth of the AT: the first, during the very early years of life, and the second, during puberty, approximately between the 9th to 13th years of age.[117]

The higher number of adipocytes that are present during childhood–adolescence in an obesity context could occur through several mechanisms: (1) the increase in cell number begins at an earlier age (age of onset), (2) the onset of total adipocyte number ends later in individuals with obesity, or (3) because there is an accelerated acquisition of adipocytes (augmented relative acquisition).[61] By integrating data from subjects of all ages, Spalding et al. retrospectively determined that the increase in number of adipocytes occurred significantly earlier in children with obesity, that acquisition of adipocytes was higher (augmented relative acquisition), and that the end of expansion of number of adipocytes occurred earlier in this condition[61]; thus, they were able to conclude that the number of adipocytes seen in adulthood was set earlier in subjects with obesity and that it was not caused by a prolonged expansion period. Although the evidence points towards the earlier life as the period that most likely contributes to increased cellularity, based on the cross-sectional study design, the authors could not exclude the possibility that individuals who gradually gain weight over the years, may initially increase their adipocyte size until a threshold is reached,[61] after which recruitment of new fat cells from committed precursor cells or MSC could take place.

Insights into childhood obesity can be derived indirectly from Genome-Wide Association Studies (GWAS). Recent data from these studies have identified multiple gene variants associated to various forms of childhood obesity.[118–120] The most common loci linked to both monogenic and polygenic forms of early-onset obesity are related to hypothalamic function and the regulation of food intake (MC4R, LEP, LEPR, POMC, and PCSK1). Consequently, these studies indicate that early adiposity arises from energy imbalances, resulting in excessive lipid accumulation, progressive adipocyte hypertrophy, and a reset of the number of mature adipocytes during adolescence.

Most previous clinical-genetic studies have suggested that early-onset adiposity, to some extent, is a consequence of hyperphagia that subsequently affects AT biology.[121,122] However, these human studies do not provide insights into the molecular adaptations occurring within AT in response to an energy surplus during early developmental stages. Therefore, examining animal models that investigate AT biology during development could assist in understanding the mechanisms involved in adipocyte dynamics and their implications for obesity risk.

7 | USING OF ANIMAL MODELS TO STUDY CHILDHOOD OBESITY

Obesity in children is relatively a "recent" health problem and, together with the ethical limitations and pediatric age, is not easy one

to study. This is why the use of animal models to complete the missing information in this important field is proving to be very helpful. For example, the reduced lifespan of rodent models is very valuable for addressing the study of WAT dynamics in the pediatric age and their long-term impact, especially considering that early postnatal life is the period with the highest adipogenesis rate.[60]

To determine in vivo the role of the adipogenic and lipogenic components during early life, Pouteau et al.[60] studied the AT dynamics in lean and genetically obese Zucker rats, from the suckling period to puberty (which corresponds from infant period to adolescence in humans) with the use of deuterated water. Authors analyzed the inguinal (scWAT), mesenteric, perigonadal, and retroperitoneal (vWAT) depots and determined cell proliferation, TAG synthesis and de novo lipogenesis (DNL). The highest fractional rates of cellular proliferation, TAG synthesis and DNL took place during early suckling in all rats. Importantly, a significant effect of age was noticeable in the cellular proliferation rate, as young pups at Day 13 showed a two-fold greater proliferation rate of adipose cells in all fat depots as compared with those later in life, highlighting again that early childhood as the most important period for adequate cellularity development of WAT. Cellular proliferation rates of all fat depots decreased considerably at Day 20 of life and almost plateaued thereafter indistinctly if rats where lean or obese.[60] The appearance of excessive fat mass in this model of obesity was first shown through a significant increase in DNL at the end of lactation period; suggesting that adipocyte lipid accretion is the most important mechanism for WAT expansion (in the context of obesity) in the later neonatal period. TAG synthesis was enhanced in rats with obesity from the end of suckling until Day 55, suggesting that after the accelerated growth of neonatal period, hypertrophy is the main mechanism through which excessive WAT accrual occurs.[60]

Moreover, rats with obesity showed an increased cell proliferation rate in subcutaneous, inguinal, mesenteric, epididymal, and retroperitoneal WAT depots, with the epididymal (eWAT) having the highest mean proliferation. Interestingly, at Day 55, "pubescent" rats with obesity still showed a higher proliferation rate than the lean ones in epididymal and retroperitoneal fat depots.[60] Overall, these findings suggest that WAT growth occurred during early childhood (lactation period) through an elevated hyperplasia, followed by a high hypertrophy during later childhood and puberty. In this model, obesity started to develop at the end of the lactation period, and rats with obesity showed an increased DNL and displayed higher cellular proliferation rates than lean ones in all the analyzed WAT depots at any time period. These findings suggest that if obesity develops during childhood and adolescence, an "excessive" number of adipocytes will be recruited, establishing a higher cellularity that most probably will be maintained through individual's future life.

It has been reported that WAT depots of C57Bl/6 mice exposed to an HFD responded differently depending on the age of exposure to the nutritional challenge. If exposure was initiated at 4 weeks of age, obesity in mice was accompanied by an increased adipogenesis rate; nevertheless, this was not the case when the nutritional challenge was initiated at 10 weeks of age, and adult mice exposed to HFD did not exhibit an increased adipogenesis rate despite gaining a similar amount of weight.[50] The authors also studied WAT adipogenesis rate in the Leprdb/Leprdb (db/db) mouse model during growth. At 4 weeks old, db/db mice showed an increased adipocyte labeling of the sWAT and vWAT depots when compared with wild-type mice under a similar background. Importantly, these effects were not observed in adult db/db mice; suggesting that in this mouse model, an increased adipogenesis rate during the youngest age contributed in an important manner to the development of the obese phenotype.

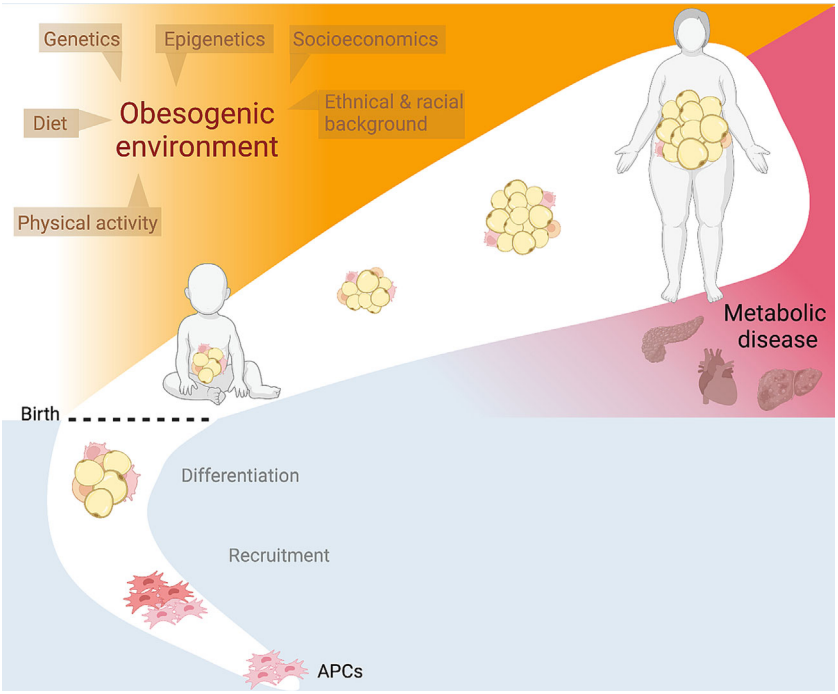

FIGURE 4 WAT development from intrauterine life to adulthood. White adipose tissue (WAT) depots develop during gestation and early life from mesenchymal stem cells, which then firstly commit to the adipocyte lineage followed by terminal differentiation of adipocyte progenitor cells (APCs) into adipocytes. In an obesogenic environment, excess energy is accumulated into the WAT. WAT initially expands through hypertrophy. Under a chronic energy excess, de novo adipogenesis takes place, at least during growth periods (i.e., childhood and puberty), leading to a higher adipocyte number that will be maintained through the rest of the individual's lifespan.

Overall, results from diet-induced or genetically induced obesity mouse models show the importance of cellular and lipid turnover during the growth period of individuals in an obesity context.[50,60]

8 | CONCLUSION AND PERSPECTIVES

The factors determining fat mass as well as WAT dynamics in children are far from being understood, and further research is required urgently. So far, the most important period for adipogenesis occurs during childhood and adolescence and when the number of total adipocytes is set.[50,60,61,87] Hence, obesity is established during childhood and/or adolescence; it is currently proposed that (1) a higher number of total adipose cells will be establishes and (2) subsequently maintained throughout the rest of the individual's life. Given that adipocyte turnover is relatively low, long-term maintenance of this high adipocyte set point would explain, in part, why children/adolescents with obesity are so resilient to weight loss and remain with obesity throughout life.

We suggest that the ontogeny of WAT also plays an important role in determining not only adipocyte number but also adipocyte size, and consequently cellular and metabolic features. The fact that adipocytes in the same fat depot(s) arise from different embryonic lineages forming a mosaic pattern, only remarks the great complexity of adipose cells dynamics and the important challenge for future research.

Notably, current knowledge regarding human WAT growth during childhood and adolescence, either in normal weight conditions or in obesity have mostly been obtained by cross-sectional histological assessment of WAT. Therefore, we can only make inferences about the lipid and cellular turnover during this period of life, based on experimental models. Indeed, in rodent models of obesity, this condition was developed after the earliest postnatal life, which is the period with the highest cellular proliferation rates.[52,62] Consequently, we cannot dismiss the idea that exposure to an obesogenic environment during an earlier stage of neonatal life could lead to a major recruitment of "excessive" adipocytes, setting an even higher adipocyte number that will be maintained through the rest of the individual's lifespan. At this point, we can only speculate about the impact that an increased hyperplasia and hypertrophy of WAT during first years of life might have on future WAT dynamics (Figure 4).

In conclusion, the importance of studying childhood obesity relies on several aspects such as (1) most children with obesity will remain with this condition throughout adulthood, (2) the long-term impact of childhood obesity on metabolic health and associated diseases remains largely unknown, and (3) childhood and adolescence are critical periods for adipogenesis, making it essential to investigate further. Thus, more pediatric preclinical and clinical studies as well as the development of mouse models to specifically study childhood obesity are needed. These studies should assess some key aspects including (1) the factors that determine fat mass and adipocyte dynamics from adolescence to adulthood, (2) the early factors, ranging from pregnancy to early life that influence the activity of BAT, and (3) the signals and mechanisms involved in establishing the final number of adipocyte during childhood and adolescence. These will contribute to identifying potential interventions aimed at limiting excessive adipocyte numbers during these critical periods. Moreover, they will help establish evidence-based therapeutic approaches focused on accelerating adipocyte turnover. This involves removing hypertrophic adipocytes and replacing them with newly formed, non-hypertrophic adipocytes.

9 | FUTURE DIRECTIONS

Measuring adipocyte/lipid turnover in pediatric population would be extremely important. However, the current methods relying on fat biopsy to determine lipid/adipocyte turnover pose significant ethical constraints, particularly when applied to children. Therefore, it is crucial to explore the development of noninvasive approaches for measuring these variables in children in the future. Potential approaches for measuring adipocyte/lipid turnover in children may involve tracing biomarkers in body fluids (such as blood) or utilizing innovative imaging techniques that can identify tracers without the need for sample collection.

While these novel techniques develop, better and more accurate experiments with animal models will help to better understanding of the dynamics experienced by AT during early fat accumulation and to develop novel therapeutic approaches aimed at limiting (1) early-onset hypertrophy and (2) the number of adipocytes at the end of the growth phase (i.e., adolescence).

AUTHOR CONTRIBUTIONS

Ivonne Palacios-Marin: Conceptualization; writing the original draft; writing review and editing. **Dolors Serra**: Writing-review and editing. **Marijana Todorčević**: Conceptualization; writing the original draft; writing review and editing and supervision. **Josep C. Jiménez-Chillarón**: Writing review and editing and supervision. **Laura Herrero**: Writing review and editing and supervision. Figures were created with BioRender.com.

CONFLICT OF INTEREST STATEMENT

No conflict of interest statement.

ORCID

Dolors Serra https://orcid.org/0000-0002-4936-4206
Laura Herrero https://orcid.org/0000-0003-4244-4673

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